DESCRIPTION

CRYSTAL FORM OF QUINOLINE COMPOUND AND PROCESS FOR ITS PRODUCTION

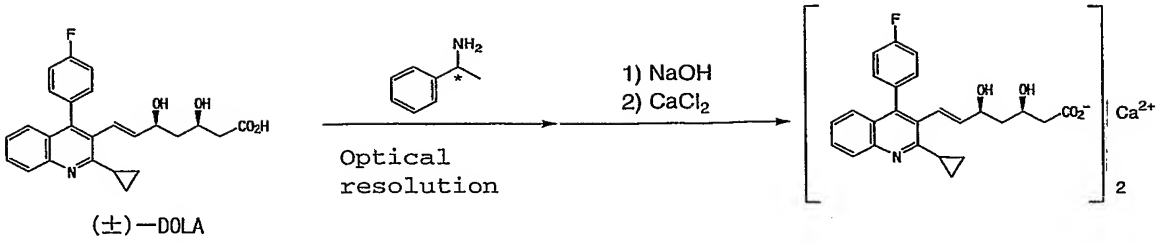
TECHNICAL FIELD

The present invention relates to a crystal form of pitavastatin calcium known by a chemical name monocalcium bis[(3*R*,5*S*,6*E*)-7-(2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl)-3,5-dihydroxy-6-heptenoate], which is useful for treatment of hyperlipemia, as a HMG-CoA reductase inhibitor, a process for its production, and a pharmaceutical composition comprising this compound and a pharmaceutically acceptable carrier.

Particularly, it relates to pitavastatin calcium in a crystal form, which is characterized by containing from 5 to 15% (W/W) of water and which is useful as a drug substance for pharmaceuticals, from the viewpoint of the stability, etc., a process for its production, and a pharmaceutical composition containing it.

BACKGROUND ART

Pitavastatin calcium (see Patents Documents 1, 2 and 3) is commercially available as an antihyperlipemic treating agent, and as its production method, a method of optical resolution employing optically active α-methylbenzylamine has already been reported (see Patent Document 4 and Non-patent Document 1).



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Known as methods for producing the compound of the formula (3) as the starting material, are:

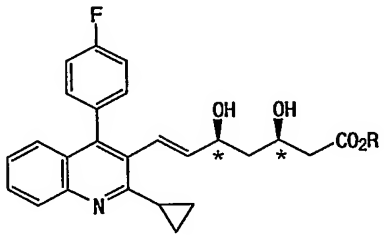
·column chromatographic separation employing an optical isomer separation column (see Patent Document 5),

·asymmetric synthesis (see Patent Documents 6 and 7),

·method of subjecting to chemical syn reduction a compound of the formula (4) which may be produced by using chiral synthon (see Patent Document 8),

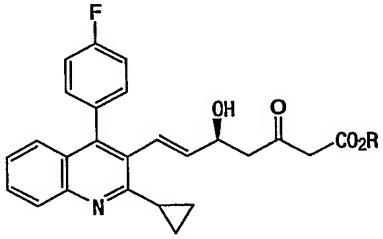
·method of subjecting to a biological syn reduction a compound of the formula (4) (see Patent Document 9), and

·optical resolution employing an enzyme (see Patent Document 10).



(3)

wherein R is a C_{1-4} alkyl group.



(4)

wherein R is a C_{1-4} alkyl group.

Patent Document 1: JP-A-1-279866

Patent Document 2: EP304063A

Patent Document 3: U.S. Patent No. 5,011,930

Patent Document 4: JP-A-5-148237

Patent Document 5: WO95/23125

Patent Document 6: WO03/042180

Patent Document 7: JP-A-8-092217

Patent Document 8: JP-A-8-127585

Patent Document 9: JP-A-2002-300897

Patent Document 10: JP-A-13-352996

Non-patent Document 1: Bioorganic & Medicinal Chemistry Letters, 9 (1999), p. 2977

DISCLOSURE OF THE INVENTION

A drug substance for pharmaceuticals is desired to have high quality and a stable crystal form from the viewpoint of the storage and is further required to be durable for the production in a large scale. However, in the conventional method for producing pitavastatin calcium, there has been no disclosure relating to the water content or the crystal form. It has been found that if pitavastatin calcium (crystal form A) is subjected to drying in a usual manner, the crystallinity will decrease to a state close to an amorphous state as shown in Fig. 2 when the water content becomes to be at most 4%, even with one which shows the powder X-ray diffraction as shown in Fig. 1 prior to the drying.

Further, it has been found that the pitavastatin calcium which has become amorphous, has very poor stability during the storage, as shown in Table 1.

TABLE 1: Stability data of drug substance (influence of the water content)

Storage conditions	Measured item	Storage period			
		Initial stage	30 Days	60 Days	90 Days
40°C air tight	Water content (%)	7.89	7.85	7.88	7.81
	Analogous substance (%)	0.179	0.208	0.189	0.211
	Pitavastatin calcium (%)	99.38	99.42	99.79	99.64
Open air	Water content (%)	7.89	2.45	1.99	1.77
	Analogous substance (%)	0.179	0.742	1.347	2.099
	Pitavastatin calcium (%)	99.38	99.26	97.19	96.49

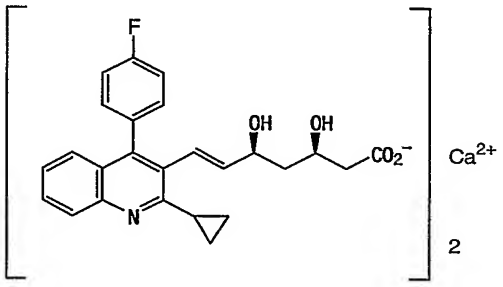
It is an object of the present invention to provide a crystalline drug substance of pitavastatin calcium which is stable even if it is not stored under a special storage condition and further to make industrial mass production possible.

The present inventors have conducted an extensive study on the interrelation between the moisture and the stability of the drug substance and as a result, have found that the stability of pitavastatin calcium can be remarkably improved by controlling the water content in

the drug substance within a specific range. Further, it has been found that there are three types of crystal forms having the same water content, and among them, crystal (crystal form A) characterized by the powder X-ray diffraction measured by using CuKα rays, is most preferred as a drug substance for pharmaceuticals. The present invention has been accomplished on the basis of these discoveries.

Namely, the present invention provides:

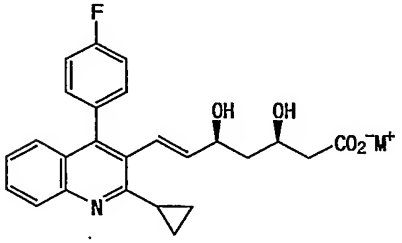
1. Crystal (crystal form A) of a compound of the formula (1):



(1)

which contains from 5 to 15% of water and which shows, in its X-ray powder diffraction as measured by using CuKα radiation, a peak having a relative intensity of more than 25% at a diffraction angle (2θ) of 30.16°.

2. A process for producing the crystal (crystal form A) as defined in Item 1, which comprises adding a calcium compound to a compound of the formula (2):



(2)

wherein M^+ represents an alkali metal ion, dissolved in water or in a C_{1-4} alcohol containing at least 60% of water.

3. A method for producing a drug substance of the crystal (crystal form A) as defined in Item 1, which comprises adjusting the water content to a level of from 5 to 15%.

4. A pharmaceutical composition which contains the crystal (crystal form A) as defined in Item 1.

The two types of crystal forms other than crystal form A are represented by crystal forms B and C, but neither of them shows peaks at diffraction angles 10.40°, 13.20° and 30.16° characteristic to crystal form A, thus indicating that they are crystal polymorphs. It was apparent that they are poor in filterability, require strict drying conditions (likely to undergo a change in the crystal form during the drying), are likely to include an inorganic substance such as NaCl, and are not necessarily able to maintain the reproducibility in the control of the crystal form. Thus, they have many drawbacks from the viewpoint of the industrial production method, and crystal form A is the best as a drug substance for pharmaceuticals.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a powder X-ray diffraction pattern of crystal form A wherein the water content is 8.78%.

Fig. 2 is a powder X-ray diffraction pattern, when the crystals used in Fig. 1 are dried to bring the water content to be 3.76%.

BEST MODE FOR CARRYING OUT THE INVENTION

Now, the present invention will be described in detail.

Pitavastatin calcium having crystal form A is characterized by its powder X-ray diffraction pattern.

Diffraction angle (2θ) (°)	d-lattice spacing	Relative intensity (>25%)
4.96	17.7999	35.9
6.72	13.1423	55.1
9.08	9.7314	33.3
10.40	8.4991	34.8
10.88	8.1248	27.3
13.20	6.7020	27.8
13.60	6.5053	48.8
13.96	6.3387	60.0
18.32	4.8386	56.7
20.68	4.2915	100.0
21.52	4.1259	57.4
23.64	3.7604	41.3
24.12	3.6866	45.0
27.00	3.2996	28.5
30.16	2.9607	30.6

Apparatus:

Powder X-ray diffraction measuring apparatus: MXLabo (manufactured by MacScience)

Ray source: Cu, wavelength: 1.54056A, Goniometer: Vertical Goniometer

Monochrometer: Used, Auxiliary means: Nil, X-ray tube voltage: 50.0 Kv, Tube current: 30.0 mA

Measuring method:

Prior to the measurement, X-ray tube alignment is tested by using silicon (standard substance).

About 100 mg of a sample is put on a glass plate for the sample and flattened, followed by measurement under the following conditions.

Range of data: from 3.0400 to 40.0000 deg,

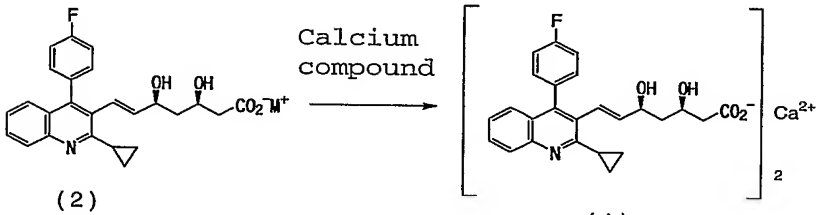
Number of data points: 925

Scanning axis: 2θ/θ, θ axis angle: No setting

Sampling interval: 0.0400 deg,

Scanning speed: 4.800 deg/min

The present invention also provides a production process to control pitavastatin calcium to have crystal form A.

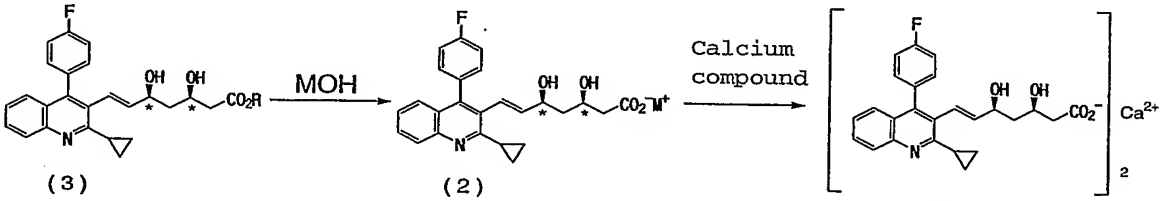


(2) (1)

The starting material is an alkali metal salt of pitavastatin shown by the formula (2), and the alkali metal may, for example, be lithium, sodium or potassium, preferably sodium.

As the calcium compound, calcium chloride or calcium acetate may, for example, be preferred, and its amount is within a range of from 0.3 to 3 mols, preferably from 0.5 to 2 mols, per mol of the compound of the formula (2).

The alkali metal salt of pitavastatin of the formula (2) may not necessarily be isolated. For example, the Ca salt may be produced as continued from the reaction of hydrolyzing e.g. a compound of the formula (3).



(3) (2) (1)

As a solvent to be used, water or a C_{1-4} alcohol containing at least 60% of water, is preferred. The C_{1-4} alcohol may, for example, be methyl alcohol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, isobutyl alcohol, sec-butyl alcohol or tert-butyl alcohol.

The amount of the solvent to be used, is usually within a range of from 3 to 100 times by mass, preferably within a range of from 5 to 30 times by mass, to the amount of the compound of the formula (2).

The crystallization temperature is not particularly limited, but it is usually within a range of from -10 to 70°C, preferably within a range of from -5 to 40°C, more preferably within a range of from 0 to 20°C.

The crystallization time is not particularly limited, but a crystallization time of from about 30 minutes to 15 hours, is usually sufficient.

As a method for crystallization, a method of carrying out the crystallization in a standing still

state, or a method of carrying out the crystallization with stirring, may, for example, be mentioned. However, it is preferred to carry out the crystallization with stirring.

Further, seed crystals of crystal form A may be used as the case requires.

Precipitated crystals will then be filtered and dried. In the present invention, it is very important to adjust the water content. The drying temperature is not particularly limited, but is preferably within a range of from 15 to 40°C.

The water content is adjusted so that it will finally be within a range of from 5 to 15% (W/W), preferably within a range of from 7 to 15% (W/W), more preferably within a range of from 7 to 13% (W/W), most preferably within a range of from 9 to 13% (W/W).

The obtained pitavastatin calcium will be pulverized and then used as a drug substance for pharmaceuticals.

Administration of the compound of the present invention may, for example, be parenteral administration in the form of an injection drug (subcutaneous, intravenous, intramuscular or intraperitoneal injection), an ointment, a suppository, an aerosol or the like, or oral administration in the form of tablets, capsules, granules, pills, a syrup drug, a liquid drug, an emulsion drug or a suspension drug.

A pharmaceutical or veterinary medicine composition

containing the compound of the present invention, contains from about 0.001 to 30%, preferably from about 0.01 to 10% of the compound of the present invention, based on the weight of the total composition.

In addition to the compound of the present invention or the composition containing such a compound, other pharmaceutically or veterinary medicinary active compound may be incorporated.

The clinical dosage of the compound of the present invention may vary depending upon e.g. the age, the body weight, the sensitivity of the patient or the degree of symptom. However, the effective dosage is usually at a level of from 0.003 to 100 mg, preferably from 0.01 to 10 mg, per day for an adult. However, if necessary, a dosage outside this range may be employed.

The compound of the present invention may be formulated for administration in accordance with a common method for preparation of medicines. Namely, tablets, capsules, granules or pills for oral administration may be formulated by using, for example, an excipient, such as sucrose, lactose, glucose, starch or mannitol; a binder, such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth, methyl cellulose or polyvinylpyrrolidone; a disintegrant, such as starch, carboxymethyl cellulose or its calcium salt, fine crystal cellulose, or polyethylene glycol; a lubricant, such as talc, magnesium or calcium stearate,

or silica; a lubricating agent, such as sodium laurate or glycerol.

An injection drug, a liquid drug, an emulsion drug, a suspension drug, a syrup drug and an aerosol drug may be prepared by using, for example, a solvent for the active ingredient, such as water, ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol or polyethylene glycol; a surfactant, such as sorbitan fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylene ether of hydrogenated castor oil, or lecithin; a suspending agent, such as carboxymethyl sodium salt, or a cellulose derivative such as methyl cellulose, tragacanth, a natural rubber such as gum arabic; a preservative, such as a p-hydroxybenzoate, benzalkonium chloride or a sorbic acid salt.

For an ointment which is a percutaneous absorption type formulation, white petrolatum, liquid paraffin, a higher alcohol, macrogol ointment, hydrophilic ointment or an aqueous gel base material may, for example, be used.

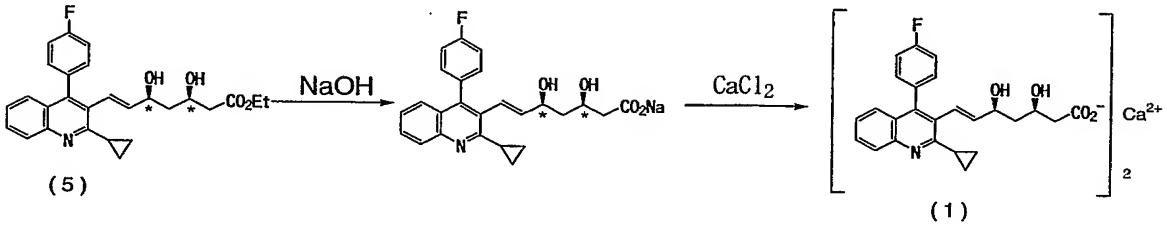
A suppository may be prepared by using e.g. cacao butter, polyethylene glycol, lanolin, fatty acid triglyceride, coconut oil or polysorbate.

Now, the present invention will be described in further detail with reference to Example. However, it should be understood that the present invention is by no

means restricted to such a specific Example.

The compound (5) used in the Example was prepared in accordance with the method disclosed in WO95/23125.

EXAMPLE 1



(5) (1)

2.71 kg (6.03 mol) of the compound (5) was dissolved in 50 kg of ethanol with stirring, and after confirming the solution to be a uniform solution, 58.5 kg of water was added. After cooling it to from -3 to 3°C, 3.37 liters of a 2 mol/liter sodium hydroxide aqueous solution was dropwise added thereto, followed by stirring at the same temperature for 3 hours to complete the hydrolytic reaction. In order to introduce the entire amount of the sodium hydroxide aqueous solution to the reaction system, 4.70 kg of water was used.

The reaction mixture was distilled under reduced pressure to remove the solvent, and after removing 52.2 kg of ethanol/water, the internal temperature was adjusted to from 10 to 20°C. Into the obtained concentrated solution, a separately prepared calcium chloride aqueous solution (95% $CaCl_2$ 775 g/water 39.3 kg, 6.63 mol) was dropwise added over a period of 2 hours. In order to introduce the entire amount of the calcium chloride aqueous solution into the reaction system, 4.70

kg of water was used. After completion of the dropwise addition, stirring at the same temperature was continued for 12 hours, whereupon precipitated crystals were collected by filtration. The crystals were washed with 72.3 kg of water and then dried under reduced pressure in a drier at 40°C while paying an attention to the product temperature until the water content became 10%, to obtain 2.80 kg (yield: 95%) of pitavastatin calcium as white crystals.

The powder X-ray diffraction was measured to confirm the crystals to be crystal form A.

INDUSTRIAL APPLICABILITY

According to the present invention, an industrial method for producing a crystalline drug substance of pitavastatin calcium excellent in stability, has been established.